

Convergence of recent GWAS data for suicidality with previous blood biomarkers: independent reproducibility using independent methodologies in independent cohorts

Alexander B. Niculescu, III ^{1,2,3} and Helen Le-Niculescu ¹

1. Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA
2. Stark Neuroscience Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA
3. Indianapolis VA Medical Center, Indianapolis, IN, USA

ABSTRACT

Recent genetic studies for suicidality, including four independent GWAS, have not reproduced each other's top implicated genes. While arguments of heterogeneity, methodology, and sample sizes can be invoked, heterogeneity is a feature, not a "bug" (as is well understood in biology and in personalized medicine). A comprehensive body of work on blood biomarkers for suicidality has previously been published by our group. We examine the issue of reproducibility using these different approaches, and provide reassuring evidence for convergence of findings, as well as some generalizable insights.

"To know things as they are is better than to believe things as they seem"

- Tom Wicker

This is the author's manuscript of the article published in final edited form as:

Niculescu, A. B., & Le-Niculescu, H. (2020). Convergence of recent GWAS data for suicidality with previous blood biomarkers: Independent reproducibility using independent methodologies in independent cohorts. *Molecular Psychiatry*, 25(1), 19–21.
<https://doi.org/10.1038/s41380-019-0465-6>

Our group has published a series of papers in Molecular Psychiatry identifying blood gene expression biomarkers that track suicidal ideation in a discovery cohort, are validated in a suicide completers cohort, and predict suicidal ideation state, and future hospitalizations for suicidality, in independent cohorts [1,2,3].

Since our last publication in 2017, a series of 4 GWAS of suicidality (ideation, attempts) [4,5,6,7], as well as a family based genetic study of suicide completers [8] and a family based genetic study in suicide attempters [9], have been published, in Molecular Psychiatry and other journals.

We endeavored to examine the issue of convergence of those studies with our previous work (Table 1). Of note, there was no overlap between the top genes implicated by these different recent genetic studies, which raises the issue of apparent lack of reproducibility in the field. We compared the list of top genes implicated by each of the recent genetic studies (genes that were associated with loci/SNPs that were statistically significant and/or were highlighted/discussed by the authors in their paper) [4,5,6,7,8,9], with the list of candidate biomarkers that survived the initial whole-genome discovery step in our previous published studies, before any literature-based prioritization. We sought to see if any of the top genes from the recent genetic studies have functional evidence of tracking suicidal ideation in our blood gene expression biomarker discovery studies.

Table 1.

Genetic studies		Biomarker studies			
Study Phenotype (Discovery cohorts)	Top genes implicated	Niculescu et al. [3] Suicidal Ideation (Universal Within- subject $n = 66$)	Niculescu et al. [3] Suicidal Ideation (Male bipolar Within- subject $n = 20$)	Levey et al. [2] Suicidal Ideation (Females Within- subject $n = 12$)	Niculescu et al. Suicidal Ideation (Males [1] Within- subject $n = 37$)
GWAS					
Levey et al. [7] Severity of suicide attempt (Yale-Penn European Americans (EAs, $n = 2439$) and African Americans (AAs, $n = 3881$))	LDHB ARNTL2- AS1 FAH CTXND1 PGBD5 NARG2 PHLDB2	LDHB PHLDB2 PGBD5	PGBD5	FAH PHLDB2	PHLDB2
Kimbrel et al. [5] Suicide ideation, Suicide attempt (US Military Veterans; Suicide ideation $n = 138/1433$; Suicide attempt $n = 122/1447$)	KCNMB2 ABI3BP LUZP2	KCNMB2 ABI3BP	LUZP2	KCNMB2	ABI3BP LUZP2
Erlangsen et al. [6] Suicide attempt (Danish population, $n = 6024/44,240$)	PDE4B FAM114A2 RBFOX2 PREX1 KIAA1549L	PDE4B FAM114A2 RBFOX2	PDE4B FAM114A2 RBFOX2	PDE4B	RBFOX2 PREX1
Stein et al. [4] Suicide attempt (US Military $n = 473/9778$)	MRAP2 CEP162	CEP162		CEP162	CEP162

Genetic studies		Biomarker studies			
Family-based genetic studies					
Coon et al. [8] Suicide completers (43 Utah high-risk families, with an average of 6.2 suicides per family)	207 genes	72/207 (34.8%) ACSL6 LACTB PRKAG2 AGBL2 GIMAP1 GIMAP7 HTR2A al.	63/207 (30.4%) NUB1 MTNR1A STAT1 SP140 ABCB8 SLC7A1 HTR2A al.	89/207 (43%) FNDC3A ETV2 ADAM10 RCBTB2 CYP4V2 GIMAP4 HTR2A al.	65/207 (31.4%) SLC7A1 GIMAP5 AQP9 ALDH1A2 PRKAG2 RHEB MSRA al.
Sokolowski et al. [9] Suicide attempt (Ukraine population, family based study, trios, N = 498 offspring with medically severe suicide attempt)	CACHD1 CACNA1D CR1 CRISPLD2 GABRR2 GNAS GRIN2B GSN MAP3K9 PFN2 PRSS3 RALGPS1 RETREG1 RNASEH2B SYTL3 TSPAN2 UBE2H	CACNA1D CR1 GRIN2B GSN RALGPS1 RNASEH2B SYTL3 UBE2H	CR1 GNAS GSN MAP3K9 RALGPS1 RNASEH2B SYTL3 TSPAN2 UBE2H	PRSS3 RALGPS1 TSPAN2	CACNA1D CR1 CRISPLD2 GNAS GSN RALGPS1 RNASEH2B SYTL3 TSPAN2 UBE2H

As illustrated in Table 1, there is a remarkable overlap with the universal candidate biomarkers described in our 2017 study (where we combined gender and psychiatric diagnosis). The overlap is even greater when we include all of our previous studies/analyses, conducted separately in males, females, and male bipolars. While statistical calculations could be made, the over-representation in the overlaps shown in

Table 1 is self-evident (as a small number of genetic findings are highlighted in each genetic study, and a fraction of the genome has gene expression changes tracking suicidality in each of the biomarker studies). The important points are biological (functional evidence), and methodological (reproducibility). Reproducibility of findings, across independent laboratories, using independent cohorts, and different methodologies, is the litmus test in science [10]. These results are thus reassuring for the field.

On a methodological note, it is possible that different approaches have different sample size requirements, and different challenges in accruing those sample sizes. As we show here, our within-subject longitudinal gene expression studies tracking a quantitative phenotype (severity of suicidal ideation), conducted with dozens of subjects, are comparable to larger family based genetic studies for a strong categorical phenotype (suicide completion), with hundreds of subjects, and to case-control genetic (GWAS) studies conducted with thousands or tens of thousands of subjects.

Of interest, the genes that overlap between our biomarker studies and the genetic studies were by and large not among the top predictive biomarkers for suicidality identified by us at the end of our biomarker studies [1,2,3]. It is possible that SNP-level signal strength and reproducibility, as are assessed in GWAS, tag genes that are more invariant and perhaps involved in less-specific, housekeeping type functions, as opposed to the genes identified by expression studies looking at functional ability to track and predict a phenotype. The latter may identify genes that are more specific for a phenotype and more variable at a SNP level due to evolutionary fine tuning and adaptation to the environment, especially in the case of complex behavioral phenotypes like suicidality.

Suicidality (ideation, attempts, completions) is a heterogeneous phenotype, likely on a spectrum of severity [3], with a strong environmental component, and with biological gender and diagnostic differences [1,2,3]. It is likely that our blood biomarkers reflect the effects of many different SNPs, are at the interface of genes and environment, and thus capture more of the biology. Beyond their practical applicability, they can serve as a Rosetta Stone and integrator of independent genetic studies [11].

REFERENCES

1. Niculescu, A. B., Levey, D. F., Phalen, P. L., Le-Niculescu, H., Dainton, H. D., Jain, N., Belanger, E., James, A., George, S., Weber, H., Graham, D. L., Schweitzer, R., Ladd, T. B., Learman, R., Niculescu, E. M., Vanipenta, N. P., Khan, F. N., Mullen, J., Shankar, G., ... Salomon, D. R. (2015). Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Molecular Psychiatry*, 20(11), 1266–1285. <https://doi.org/10.1038/mp.2015.112>
2. Niculescu, A. B., & Le-Niculescu, H. (2020). Convergence of recent GWAS data for suicidality with previous blood biomarkers: Independent reproducibility using independent methodologies in independent cohorts. *Molecular Psychiatry*, 25(1), 19–21. <https://doi.org/10.1038/s41380-019-0465-6>
3. Niculescu, A. B., Le-Niculescu, H., Levey, D. F., Phalen, P. L., Dainton, H. L., Roseberry, K., Niculescu, E. M., Niezer, J. O., Williams, A., Graham, D. L., Jones, T. J., Venugopal, V., Ballew, A., Yard, M., Gelbart, T., Kurian, S. M., Shekhar, A., Schork, N. J., Sandusky, G. E., & Salomon, D. R. (2017). Precision medicine for suicidality: From universality to subtypes and personalization. *Molecular Psychiatry*, 22(9), 1250–1273. <https://doi.org/10.1038/mp.2017.128>
4. Stein, M. B., Ware, E. B., Mitchell, C., Chen, C.-Y., Borja, S., Cai, T., Dempsey, C. L., Fullerton, C. S., Gelernter, J., Heeringa, S. G., Jain, S., Kessler, R. C., Naifeh, J. A., Nock, M. K., Ripke, S., Sun, X., Beckham, J. C., Kimbrel, N. A., Ursano, R. J., & Smoller, J. W. (2017). Genomewide association studies of suicide attempts in US soldiers. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 174(8), 786–797. <https://doi.org/10.1002/ajmg.b.32594>
5. Kimbrel, N. A., Garrett, M. E., Dennis, M. F., Hauser, M. A., Ashley-Koch, A. E., & Beckham, J. C. (2018). A genome-wide association study of suicide attempts and suicidal ideation in U.S. military veterans. *Psychiatry Research*, 269, 64–69. <https://doi.org/10.1016/j.psychres.2018.07.017>
6. Kimbrel, N. A., Garrett, M. E., Dennis, M. F., Hauser, M. A., Ashley-Koch, A. E., & Beckham, J. C. (2018). A genome-wide association study of suicide attempts and suicidal ideation in U.S. military veterans. *Psychiatry Research*, 269, 64–69. <https://doi.org/10.1016/j.psychres.2018.07.017>

7. Levey, D. F., Polimanti, R., Cheng, Z., Zhou, H., Nuñez, Y. Z., Jain, S., He, F., Sun, X., Ursano, R. J., Kessler, R. C., Smoller, J. W., Stein, M. B., Kranzler, H. R., & Gelernter, J. (2019). Genetic associations with suicide attempt severity and genetic overlap with major depression. *Translational Psychiatry*, 9(1), 1–12. <https://doi.org/10.1038/s41398-018-0340-2>
8. Coon, H., Darlington, T. M., DiBlasi, E., Callor, W. B., Ferris, E., Fraser, A., Yu, Z., William, N., Das, S. C., Crowell, S. E., Chen, D., Anderson, J. S., Klein, M., Jerominski, L., Cannon, D., Shabalin, A., Docherty, A., Williams, M., Smith, K. R., ... Gray, D. (2018). Genome-wide significant regions in 43 Utah high-risk families implicate multiple genes involved in risk for completed suicide. *Molecular Psychiatry*, 1–14. <https://doi.org/10.1038/s41380-018-0282-3>
9. Sokolowski, M., Wasserman, J., & Wasserman, D. (2018). Gene-level associations in suicide attempter families show overrepresentation of synaptic genes and genes differentially expressed in brain development. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 177(8), 774–784. <https://doi.org/10.1002/ajmg.b.32694>
10. Niculescu, A. B., Levey, D., Le-Niculescu, H., Niculescu, E., Kurian, S. M., & Salomon, D. (2015). Psychiatric blood biomarkers: Avoiding jumping to premature negative or positive conclusions. *Molecular Psychiatry*, 20(3), 286–288. <https://doi.org/10.1038/mp.2014.180>
11. Ayalew, M., Le-Niculescu, H., Levey, D. F., Jain, N., Changala, B., Patel, S. D., Winiger, E., Breier, A., Shekhar, A., Amdur, R., Koller, D., Nurnberger, J. I., Corvin, A., Geyer, M., Tsuang, M. T., Salomon, D., Schork, N. J., Fanous, A. H., O'Donovan, M. C., & Niculescu, A. B. (2012). Convergent functional genomics of schizophrenia: From comprehensive understanding to genetic risk prediction. *Molecular Psychiatry*, 17(9), 887–905. <https://doi.org/10.1038/mp.2012.37>